Critical Care

REVIEW

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A narrative review on the future of ARDS: evolving definitions, pathophysiology, and tailored management

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Abstract

Acute respiratory distress syndrome (ARDS) is a severe complication of critical illness, characterized by bilateral lung infiltrates and hypoxemia. Its clinical and pathophysiological heterogeneity poses challenges for both diagnosis and treatment. This review outlines the evolution of ARDS definitions, discusses the underlying pathophysiology of ARDS, and examines the clinical implications of its heterogeneity. Traditional ARDS definitions required invasive mechanical ventilation and relied on arterial blood gas measurements to calculate the PaO_2/FiO_2 ratio. Recent updates have expanded these criteria to include patients receiving noninvasive respiratory support, such as high-flow nasal oxygen, and the adoption of the SpO_2/FiO_2 ratio as an alternative to the PaO_2/FiO_2 ratio. While these changes broaden the diagnostic criteria, they also introduce additional complexity. ARDS heterogeneity—driven by varying etiologies, clinical subphenotypes, and underlying biological mechanisms—highlights the limitations of a uniform management approach. Emerging evidence highlights the presence of distinct ARDS subphenotypes, each defined by unique molecular and clinical characteristics, offering a pathway to more precise therapeutic targeting. Advances in omics technologies—encompassing genomics, proteomics, and metabolomics—are paving the way for precision-medicine approaches with the potential to revolutionize ARDS management by tailoring interventions to individual patient profiles. This paradigm shift from broad diagnostic categories to precise, subphenotype-driven care holds promise for redefining the landscape of treatment for ARDS and, ultimately, improving outcomes in this complex, multifaceted syndrome.

Keywords Acute respiratory distress syndrome, Pathophysiology, Omics, Heterogeneity, Subphenotype, Personalized medicine

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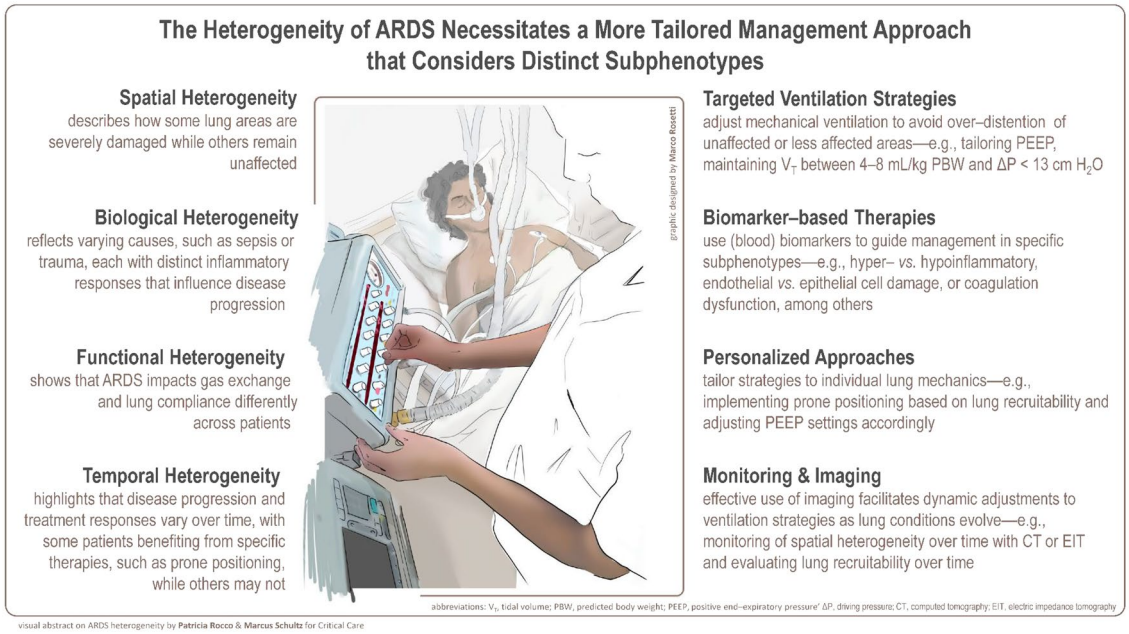
Graphical abstract


The Heterogeneity of ARDS Necessitates a More Tailored Management Approach that Considers Distinct Subphenotypes
Spatial Heterogeneity
describes how some lung areas are severely damaged while others remain unaffected
Biological Heterogeneity
reflects varying causes, such as sepsis or trauma, each with distinct inflammatory responses that influence disease progression
Functional Heterogeneity
shows that ARDS impacts gas exchange and lung compliance differently across patients
Temporal Heterogeneity
highlights that disease progression and treatment responses vary over time, with some patients benefiting from specific therapies, such as prone positioning, while others may not
graphic designed by Marco Rosetti
Targeted Ventilation Strategies
adjust mechanical ventilation to avoid over–distention of unaffected or less affected areas—e.g., tailoring PEEP, maintaining V_T between 4–8 mL/kg PBW and ΔP < 13 cm H_2O
Biomarker–based Therapies
use (blood) biomarkers to guide management in specific subphenotypes—e.g., hyper– vs. hypoinflammatory, endothelial vs. epithelial cell damage, or coagulation dysfunction, among others
Personalized Approaches
tailor strategies to individual lung mechanics—e.g., implementing prone positioning based on lung recruitability and adjusting PEEP settings accordingly
Monitoring & Imaging
effective use of imaging facilitates dynamic adjustments to ventilation strategies as lung conditions evolve—e.g., monitoring of spatial heterogeneity over time with CT or EIT and evaluating lung recruitability over time
abbreviations: V_T, tidal volume; PBW, predicted body weight; PEEP, positive end–expiratory pressure' ΔP, driving pressure; CT, computed tomography; EIT, electric impedance tomography
visual abstract on ARDS heterogeneity by Patricia Rocco & Marcus Schultz for Critical Care

Introduction

Acute respiratory distress syndrome (ARDS) was initially described as a severe complication in critically ill patients, characterized by bilateral lung infiltrates unrelated to cardiac failure and sudden-onset hypoxemia [1]. Despite more than 50 years of research, ARDS remains a significant clinical challenge, with high mortality rates [1] and a rising incidence [2]. Current guidelines emphasize the importance of early recognition and effective management of ARDS. The European society of intensive care medicine (ESICM) [3] and the American thoracic society (ATS) [4] recommend lung-protective ventilation strategies, prone positioning for moderate to severe ARDS, and the selective use of adjunctive therapies, such as extracorporeal membrane oxygenation (ECMO), for specific patients [5]. Nevertheless, treatment for ARDS remains largely supportive.

The definition of ARDS has evolved through multiple updates to reflect new clinical insights and practical considerations, aiming to enhance its relevance and applicability [6]. These efforts notwithstanding, ongoing debates remain regarding the accuracy and practical utility of current definitions in clinical practice, research, and education. Integrating biomarkers and genetic profiling into ARDS definitions holds promise for personalized medicine, with the potential to shift treatment from a one-size-fits-all approach to patient-tailored strategies. Recent studies have identified specific ARDS subphenotypes, reinforcing the possibility that personalized treatments could improve outcomes and reduce risks associated with non-targeted therapies. However, current guidelines do not yet address the need for subphenotype-specific treatment strategies [4, 5].

This review provides a critical appraisal of the evolution of ARDS definitions, examining their strengths and limitations within the context of modern clinical practice and current scientific evidence. It also discusses the challenges and potential advantages of identifying and defining ARDS subphenotypes, and examines ARDS pathophysiology, clinical characteristics, and imaging features to support the development of more precise and clinically relevant diagnostic criteria. Our aim is to facilitate early recognition, improve prognostic accuracy, and optimize treatment approaches for ARDS, ultimately advancing critical care practices and improving patient outcomes.

Evolution of ARDS definitions

In 1967, ARDS was first described as a syndrome of hypoxemia, tachypnea, and reduced lung compliance resulting from various causes [7]. This initial definition underscored ARDS as a severe, treatment-resistant form of respiratory failure, facilitating early recognition and management. However, it relied heavily on clinical

signs and chest imaging alone—making it challenging to distinguish ARDS from other pulmonary conditions in its early stages—and failed to consider critical variables, such as positive end-expiratory pressure (PEEP) (Fig. 1).

In 1988, the Lung injury score (LIS) was introduced to quantify the severity of ARDS [8]. Building on the first description of ARDS, the LIS incorporated both clinical and physiological parameters and introduced key elements—PEEP level and the ratio of arterial oxygen pressure (PaO_2) to inspired oxygen fraction (FiO_2)—to quantify oxygenation impairment. Despite its innovations, the LIS was limited by its use of subjective radiographic criteria and static evaluation, which failed to capture the dynamic nature of ARDS progression.

In 1994, the American-European consensus conference (AECC) definition introduced further refinements, incorporating radiographic severity, respiratory compliance, and PEEP [9]. This definition also stratified ARDS severity by PaO_2/FiO_2 ratio, yet it retained weaknesses such as dependence on subjective radiographic interpretations and the omission of critical clinical parameters like PEEP levels and respiratory compliance, hindering a more comprehensive assessment of the syndrome.

The Berlin Definition, introduced in 2012, aimed to address these gaps. It clarified the criteria for bilateral infiltrates, specified the timing of hypoxemia onset, and reintroduced a minimum PEEP threshold [10]. Despite these advancements, the Berlin Definition was still of variable applicability, with inconsistent interpretation of radiographic criteria among clinicians. In 2015, an additional requirement was proposed for ARDS: that oxygenation impairment must persist with a minimum PEEP of 10 cmH_2O for at least 24 h [11]. While intended to ensure accurate stratification of severity, this requirement risked delaying diagnosis and intervention for patients who might benefit from more immediate treatment.

In 2016, the Kigali Modification of the Berlin Definition adapted ARDS diagnostic criteria to low-resource settings by eliminating the PEEP requirement, using $SpO_2/FiO_2 \leq 315$ as the oxygenation threshold, and allowing for lung ultrasound as a diagnostic tool [12]. The most recent global definition [6], based on the Kigali Modification, aims to standardize ARDS diagnostic criteria across diverse healthcare settings. This new framework includes noninvasive respiratory support options, such as high-flow nasal oxygen (HFNO); retains the PaO_2/FiO_2 ratios, with additional consideration of SpO_2/FiO_2; and emphasizes the use of lung ultrasound, promoting diagnostic flexibility and resource adaptability.

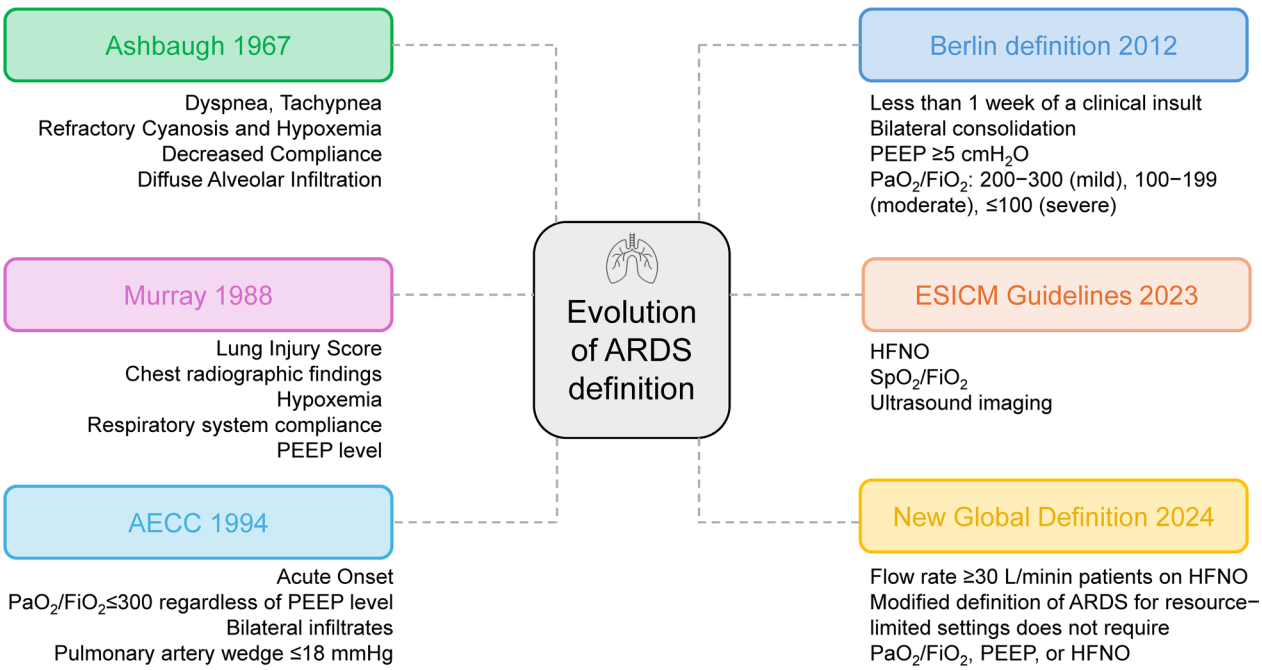


Fig. 1 Historical development of the definition of ARDS. Many investigators and organizations have made efforts towards the accurate description and identification of ARDS, beginning with Ashbaugh's description of the syndrome in 1967 and leading to the "Berlin definition" in 2012. Two new guidelines (ESICM guidelines in ARDS, 2023 and A New global definition of ARDS, 2024) have been published recently. *ARDS*, Acute respiratory distress syndrome; *PEEP*, Positive end-expiratory pressure; *PaO_2*, Arterial oxygen pressure; *FiO_2*, Fraction of inspired oxygen; *AECC*, American–European Consensus Conference, *HFNO*, High-Flow Nasal Oxygen; *SpO_2*; Peripheral oxygen saturation

Notably, all definitions to date have largely overlooked key pathophysiological parameters, potentially oversimplifying the complex pathology of ARDS. Although the latest definition acknowledges the heterogeneity of this syndrome, it remains limited in guiding treatment customization for distinct ARDS subphenotypes—a gap that could hinder efforts to tailor interventions effectively (Table 1).

Pathophysiological considerations

A comprehensive understanding of ARDS pathophysiology is essential to contextualize its diagnostic criteria and treatment approaches, providing insight into why certain interventions may benefit some patients while potentially harming others. ARDS typically begins with an initiating event, such as exposure to pathogens or cellular debris, leading to injury to the alveolar epithelium or endothelium and activation of alveolar macrophages. These macrophages release inflammatory mediators that recruit neutrophils through chemotaxis. This inflammatory cascade increases alveolar wall permeability, causing edematous fluid to accumulate in the alveolar spaces, leading to alveolar collapse and acute lung injury [13–15]. However, this simplified description overlooks several aspects of the syndrome, including its complex pathophysiology and variability in patient responses.

Spatial heterogeneity

ARDS is characterized by uneven lung damage and inflammation, with some regions severely affected by edema and consolidation while others remain relatively preserved. A study using lung CT imaging in ARDS patients demonstrated that hydrostatic pressure variations across lung regions contribute to this heterogeneity [16].

Moreover, the initial injurious stimulus disrupts endothelial integrity, causing edema and protein leakage that inactivate surfactant. Mechanical ventilation leads to cyclic recruitment and de-recruitment of alveoli, worsening lung compliance and injury. As the damaged regions expand, they exert strain on adjacent alveoli, further propagating damage and transforming otherwise homogeneous lung tissue into a patchwork of heterogeneous lesions [17].

Biological heterogeneity

Biological heterogeneity in ARDS encompasses diverse pathophysiological mechanisms and inflammatory responses across patients. Factors such as the etiology of ARDS−−whether due to sepsis, pneumonia, or trauma−−as well as individual genetic and immune responses can drive variability in disease presentation and progression [18]. ARDS etiologies are broadly categorized as either direct (primary) or indirect (secondary) lung injuries. Direct injuries, such as pneumonia, aspiration/inhalation, fat embolism, and ventilator-induced lung injury, originate within the lung and are associated with local epithelial damage [18, 19]. Indirect injuries arise from extrapulmonary insults, including sepsis, pancreatitis, burns, and drug overdose, which result in endothelial damage. While direct lung injuries are slightly more common, extrapulmonary manifestations, particularly sepsis, occur in most ARDS patients [18, 19].

Histopathological findings further distinguish ARDS etiologies, with direct injuries primarily associated with epithelial cell damage and indirect injuries impacting the endothelium. Direct injuries are also associated with more extensive alveolar collapse, fibrinous exudates, and edema within the alveolar walls [20], as well as greater hyaline membrane deposition and thicker layering [21], compared to indirect injuries.

Table 1 Pros and cons of the current definition of ARDS

	Pros	Cons
Imaging	Provides clear radiographic criteria for diagnosing bilateral infiltrates	Lacks specificity, making it difficult to differentiate ARDS from other conditions with similar imaging findings
Oxygenation	Uses an objective, easily measurable PaO_2/FiO_2 ratio to assess severity	Cutoff values may oversimplify ARDS severity and fail to account for individual variability
Mechanics	Provides a structured approach to assess ventilatory support requirements (e.g., PEEP, tidal volume)	Does not account for the physiological heterogeneity of ARDS, limiting personalized treatment strategies
Inflammation	Highlights the central role of inflammation in ARDS pathogenesis, informing therapeutic strategies	Current diagnostic biomarkers do not fully capture the complexity of inflammation in ARDS
Subphenotypes	Identify subphenotypes, which may help tailor treatment approaches	Subphenotype classification remains incomplete, limiting its clinical applicability
Mechanical ventilation	Evidence-based strategies (e.g., low tidal volume) have demonstrated clear benefits in ARDS management	Overemphasis on mechanical ventilation may overshadow other therapeutic options, such as pharmacologic interventions

Recent advancements using latent class analysis have identified two distinct ARDS subphenotypes, hyper-inflammatory and hypo-inflammatory, each exhibiting varied responses to specific therapeutic interventions [22]. This highlights the need for future approaches that integrate biological subphenotyping with clinical diagnostic criteria, enabling more personalized treatment strategies aligned with individual patient profiles.

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Functional heterogeneity

Functional heterogeneity in ARDS refers to differences in how the syndrome impacts lung function across patients. Differences are seen in gas-exchange abnormalities, lung compliance, and levels of ventilatory impairment. Some patients may experience severe hypoxemia, while others have milder oxygenation impairment, depending on the extent and location of lung injury [15]. Lung compliance variability is also common in pulmonary ARDS, often related to the degree of lung tissue damage and the presence of fluid in the alveoli [18, 23].

Heterogeneity of effects across ARDS phases

ARDS is intra-individually heterogeneous over time, exhibiting dynamic progression and an evolving response to therapeutic interventions. The distinct phases of ARDS (inflammatory/exudative and fibroproliferative) are associated with different physiological characteristics that influence the efficacy of various treatments.

For instance, the early application of prone positioning has demonstrated substantial benefits in oxygenation and survival in patients with severe ARDS, particularly during the exudative phase. This phase is characterized by increased lung recruitability and dominant inflammatory activity, enhancing the effectiveness of prone positioning [23]. Conversely, therapies such as inhaled nitric oxide, which aim to enhance oxygenation by redirecting pulmonary blood flow to ventilated regions, have shown limited efficacy across different ARDS phases and no significant mortality benefit [24]. These findings suggest that the efficacy of inhaled nitric oxide may be limited by the evolving pathophysiology of ARDS, highlighting the need for phase-specific therapeutic approaches.

Mechanical ventilation strategies also need to be personalized to address temporal changes in lung mechanics. In the early phase of ARDS, higher PEEP levels can facilitate alveolar recruitment and improve gas exchange. However, in the later phase, when lung recruitability diminishes and fibrotic changes predominate, lower PEEP levels may be necessary to prevent overdistension and associated barotrauma. This variability in recruitability over time highlights the importance of continuously adapting ventilatory strategies to the evolving disease state [25].

The variability in treatment responses over time underscores the need for personalized therapeutic strategies tailored to the phase of ARDS. Incorporating these temporal dynamics into clinical practice guidelines and future ARDS definitions could refine treatment precision and, ultimately, improve patient outcomes.

Potential implications of incorporating pathophysiology into ARDS definitions

Ventilation strategies

For many years, management of ARDS has been mainly supportive, focusing on providing adequate oxygenation while minimizing the incidence of ventilator-induced lung injury (VILI) [26–29]. Effective ventilation in ARDS requires individualized strategies that account for the underlying pathophysiology. Although standard thresholds and targets are commonly used, the heterogeneity of ARDS demands a more tailored approach [15].

Pulmonary ARDS, typically caused by direct lung injury (e.g., pneumonia or aspiration), is characterized by reduced lung compliance ($\leq$40 mL/cmH_2O), which requires low tidal volume ventilation (4–6 mL/kg predicted body weight) and higher PEEP levels (10–15 cmH_2O) to enhance oxygenation and prevent alveolar collapse. In such cases, prone positioning has proven to be particularly effective for recruiting alveoli and improving oxygenation [2].

In contrast, extrapulmonary ARDS, caused by systemic inflammation (e.g., sepsis, pancreatitis), often initially presents with higher lung compliance (>50 mL/cmH_2O), allowing for lower PEEP levels (5–10 cmH_2O) and slightly higher tidal volumes (around 6–8 mL/kg) in less severe cases. However, in more severe cases, such as those related to pancreatitis, higher PEEP may be required to optimize lung recruitability and maintain alveolar stability, despite initially preserved compliance. This variability highlights that ventilation strategies should be individualized on the basis of disease severity and lung mechanics rather than etiology alone [2].

The COVID-19 pandemic highlighted additional heterogeneity within ARDS, as patients with COVID-19-associated ARDS (CARDS) frequently exhibited high lung compliance (50–60 mL/cm H_2O) in the early stages, a notable deviation from classic ARDS presentations. Standard low-tidal-volume, high-PEEP strategies in CARDS sometimes cause ventilator overdistension, prompting adjustments. PEEP was typically set between 8 and 12 cmH_2O, with careful monitoring of driving pressures (plateau pressure minus PEEP) to avoid overdistension and barotrauma [30].

This heterogeneity highlights the necessity for ventilatory strategies tailored to each ARDS subphenotype, whether addressing the low-compliance lungs typical of pulmonary ARDS or the more compliant lungs observed in extrapulmonary ARDS and early CARDS. A one-size-fits-all ventilatory approach can lead to suboptimal outcomes, including VILI or poor oxygenation, if it does not consider these critical pathophysiological differences [31, 32].

Individualized ventilatory strategies and heterogeneity in ARDS

The heterogeneous nature of ARDS is now recognized as a significant factor influencing patient outcomes, reinforcing a shift toward precision-based treatment strategies. This refined understanding, supported by biomarker research and technologies such as machine learning, allows for a more accurate categorization of ARDS patients into distinct subphenotypes, which can predict how individual patients will respond to treatments, enabling more personalized and effective care.

Supportive strategies

Controlling tidal volume is critical, as excessive volumes can prompt inflammatory responses and increase levels of proteoglycans, such as versican and biglycan [30]. Conversely, insufficient tidal volumes can damage peripheral airways by causing uneven alveolar ventilation, which leads to localized atelectasis and alterations in interstitial fluid volume and intrathoracic pressures. These changes exacerbate shear stress and contribute to injury in smaller, less ventilated airways, thereby worsening overall lung mechanics and function [31].

PEEP improves oxygenation by reducing shunting, maintaining alveolar recruitment, and preventing extracellular matrix fragmentation. However, it can also have adverse cardiac effects, including reduced cardiac index, elevated right ventricular end-diastolic pressure, and increased pulmonary vascular resistance, which require close monitoring in ARDS patients [33]. Recent studies have shown that different ARDS subphenotypes respond differently to PEEP strategies, particularly concerning 28-day mortality [34]. Specifically, patients can be categorized into two subphenotypes: subphenotype A, which tends to have higher mortality with higher PEEP, and subphenotype B, where PEEP does not significantly impact mortality. Subphenotype A is characterized by more severe inflammation and poor oxygenation, often requiring higher PEEP to achieve optimal alveolar recruitment. In contrast, patients with subphenotype B, characterized by less inflammation and better oxygenation, may not benefit from higher PEEP and could experience exacerbated lung injury with excessive ventilation. Therefore, PEEP strategies should be tailored to the patient's clinical characteristics and their response to ventilation, with emphasis given to subphenotype-driven, personalized care (Fig. 2).

Driving pressure is another critical parameter, with elevated values associated with higher lung stress and an increased risk of mortality. Monitoring both driving and plateau pressures together provides a more comprehensive assessment of the impact of mechanical ventilation on lung function and patient outcomes [35–37]. Recruitment maneuvers (RMs), often used in low tidal volume ventilation, have not consistently improved ARDS outcomes. In some cases, prolonged RMs with high PEEP led to increased mortality, suggesting RMs may not be universally beneficial and should be employed selectively [38, 39].

The management of ARDS continues to evolve, with emerging therapies and updated guidelines shaping treatment strategies. Despite significant advancements in supportive care, such as low tidal volume ventilation and prone positioning, ARDS remains a condition with high morbidity and mortality, especially when complicated by extrapulmonary organ dysfunction, such as acute kidney injury and delirium. Recent research underscores the complex interaction between lung injury and other organ systems, highlighting the importance of early identification and tailored interventions. While corticosteroids are commonly discussed for their anti-inflammatory effects, the variability in their efficacy underscores the need for precise patient stratification. Furthermore, the growing focus on biologic therapies, including mesenchymal stromal cells and targeted biologic agents, offers potential for reducing inflammation and improving outcomes, though challenges in clinical trial design and patient heterogeneity remain significant barriers. The future of ARDS treatment lies in refining both pharmacologic and non-pharmacologic interventions to address the underlying pathophysiological mechanisms and improve long-term recovery for survivors [40].

Exploring non-conventional ventilation methods

Alternative ventilation methods such as airway pressure release ventilation (APRV), time-controlled adaptive ventilation (TCAV), and adaptive support ventilation (ASV) offer varied benefits but need further research to establish their efficacy in ARDS. Conceptually, APRV maintains alveolar patency and minimizes collapse through a high-pressure phase followed by a lower-pressure release. This mode can promote increased mean airway pressure and sustain elevated

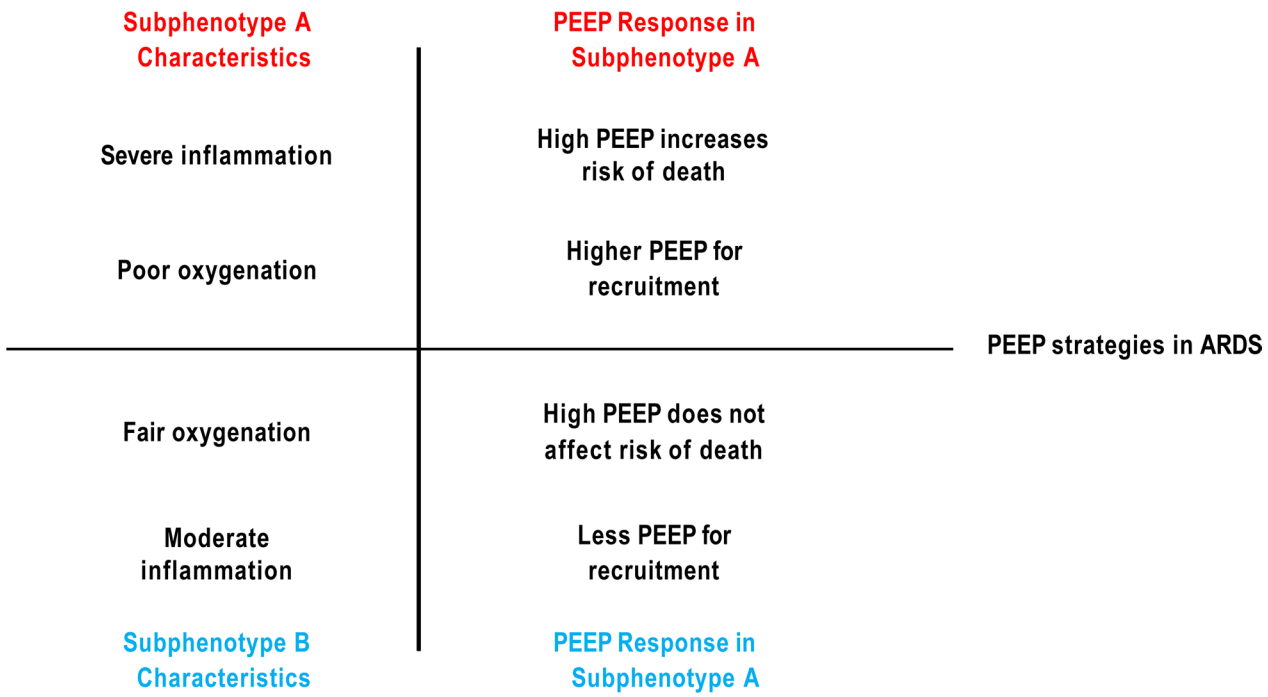

Fig. 2 Summary of PEEP (Positive End-Expiratory Pressure) Strategies in ARDS Subphenotypes A and B

pulmonary vascular resistance, potentially leading to right ventricular dysfunction, vascular injury, stress, and strain. Additionally, because APRV allows spontaneous breathing during the high-pressure phase, it may result in inadequate control of tidal volume. In a review of six randomized trials involving 360 patients, APRV was associated with improved mean arterial pressure, lower peak airway pressures, and reduced 28-day mortality, though it did not show significant oxygenation benefits. However, the risks of APRV, particularly in pediatric patients, remain an important consideration [41–43]. The TCAV protocol uses a closed-loop system designed to match lung physiology and prevent alveolar collapse. In a Wistar rat model of ARDS, TCAV was shown to reduce alveolar damage and lower inflammatory markers [44, 45]. However, the TCAV protocol assumes that inspiratory and expiratory airway resistance are equivalent—an assumption that does not hold in diseased states, where resistance often varies significantly. This discrepancy can impact the effectiveness of TCAV in pathological conditions and requires consideration when applying the protocol in clinical settings. ASV dynamically adjusts ventilation parameters based on real-time lung mechanics, benefiting ARDS patients with rapid changes in lung condition by optimizing inspiratory-to-expiratory time ratios and minimizing auto-PEEP [46]. However, the ASV algorithm can be challenged by the erratic breathing patterns often seen in the early stages of ARDS, which may disrupt its ability to provide stable, optimal ventilation and limit its effectiveness in certain clinical scenarios.

Impact of ARDS heterogeneity on precision treatment strategies: insights from recent advances

One area in which ARDS heterogeneity is particularly evident is fluid management. In patients with extrapulmonary ARDS, especially those with sepsis, aggressive fluid resuscitation may be necessary initially. However, in patients with pulmonary ARDS or those with fluid overload, a conservative approach to fluids is often more effective to prevent further deterioration of lung function [47]. Similarly, the decision to administer interventions such as corticosteroids and prone positioning should take into account the patient's ARDS subphenotype. While corticosteroids have shown mortality benefits in COVID-19 ARDS with high inflammation (type H pneumonia), they may not be beneficial—and could even be harmful—in cases with low inflammation (type L pneumonia). Prone positioning has proven beneficial in patients with severe hypoxemia and highly recruitable lung units, but it does not benefit all ARDS patients equally [48–50]. The COVID-19 pandemic highlighted this variability, with prolonged prone positioning required mainly for patients with type H pneumonia, while type L patients only needed it as a rescue measure [32].

A recent study identified three subphenotypes of severe ARDS: dry type (minimal fluid accumulation), wet type (significant fluid retention), and fibrotic type (lung fibrosis). These subphenotypes had different mortality risks and varied responses to high PEEP settings during the early phase of V-V ECMO. The wet type showed the best response to V-V ECMO, with higher PEEP settings ($\geq$10 cmH_2O) reducing 90-day in-hospital mortality. These findings suggest the need for individualized management strategies based on ARDS subphenotypes during V-V ECMO [51].

Another study identified two inflammatory subphenotypes—hyperinflammatory and hypoinflammatory—in ICU survivors with ARDS, based on plasma biomarkers predictive of outcomes and treatment responses. At discharge, the hyperinflammatory group showed more severe organ dysfunction and higher mortality, with a 30-day mortality rate of 21% versus 11% in the hypoinflammatory group, and a 1-year mortality of 48% versus 28%. These findings indicate that patients with hyperinflammatory ARDS face more pronounced derangements of coagulation, endothelial activation, and inflammation [52].

In summary, although evolving definitions of ARDS have improved our understanding of this condition, they remain limited. Past and current definitions do not fully capture the underlying pathophysiological diversity of ARDS, which varies by etiology, lung mechanics, and inflammation. This heterogeneity complicates diagnosis and treatment, with uniform strategies often resulting in suboptimal outcomes by overlooking patient-specific factors such as lung compliance, inflammatory profile, or treatment response.

ARDS is not a single disease but a spectrum, requiring more nuanced, phenotype-driven definitions and treatment frameworks. Embracing its inherent complexity through individualized approaches offers a pathway toward optimizing patient outcomes.

Knowledge gaps and future directions

As noted above, the evolving definitions and understandings of ARDS reflect efforts to improve diagnosis and tailor treatment to diverse patient needs. Traditionally, definitions like the Berlin criteria have provided a framework but are being re-evaluated to accommodate clinical variability and advances in pathophysiological understanding (Table 1). In this line, HFNO therapy [53], SpO_2/FiO_2 ratio [54], and lung ultrasound [55] have been incorporated into the new ARDS definition [3].

Right ventricular (RV) dysfunction, which is absent from the Berlin criteria, is another critical factor in ARDS assessment. A cardiopulmonary focus that includes RV function could improve outcome predictions and treatment choices, as elevated driving and transpulmonary pressures can harm the RV, leading to systemic effects such as pulmonary vasoconstriction and reduced cardiac output [56–58]. A meta-analysis of data from 1,861 patients reported RV dysfunction with higher mortality in ARDS patients [59]. Notably, low tidal volume ventilation may help protect both the lungs and the heart by reducing cyclic afterload on the RV [60].

Recent literature highlights the need for a refined ARDS definition that is adjustable to diverse clinical settings. Although the Berlin definition provides diagnostic utility, it is limited by the heterogeneity of patient profiles in ARDS studies and thus does not fully capture the inherent clinical diversity of ARDS. A more inclusive approach, which considers factors such as RV dysfunction and patient heterogeneity, is recommended. This refinement could improve risk stratification and support tailored treatment strategies, better aligning care with the diverse presentations observed across the ARDS spectrum and promoting a more personalized approach to management [61, 62].

Studies have identified distinct ARDS subphenotypes, each responding differently to treatment. These findings underscore the need for targeted approaches beyond those specified in the Berlin criteria and suggest that recognizing and addressing specific subphenotypes could optimize treatment strategies and improve patient outcomes [1, 10, 63].

One promising avenue for subphenotype differentiation is provided by omics technologies, i.e., the use of genomics, proteomics, and metabolomics to identify ARDS-specific biomarkers. Though the application of genomics in ARDS is still incipient, it offers potential for precisely assessing risk, guiding interventions, and identifying patients best suited for specific treatments. The complex genetic basis of ARDS suggests gene therapies would be of limited applicability, but genomic insights could reveal pathophysiological mechanisms and therapeutic targets [64].

Conclusions

Despite advancements in critical care, ARDS remains a complex syndrome with persistently high mortality. Our understanding of ARDS pathophysiology has grown considerably over the years, leading to refined definitions that incorporate diagnostic and prognostic criteria. Nevertheless, existing definitions and guidelines still lack specificity to fully capture the heterogeneity of ARDS. The diversity in pathophysiological pathways, clinical presentations, and responses to treatment emphasizes the need for subphenotype-based diagnostic criteria to guide more individualized interventions.

Incorporating insights from recent research on ARDS pathophysiology, alongside advancements in imaging, ventilation, and biomarker profiling, offers promising avenues to improve ARDS definitions and management strategies. Pathophysiology-driven ventilatory strategies, for instance, can address the unique needs of patients based on specific ARDS subphenotypes. By categorizing ARDS into distinct subphenotypes—such as hyper-inflammatory and hypo-inflammatory types—clinicians can adopt more personalized therapeutic strategies, potentially reducing the risks associated with one-size-fits-all approaches to treatment.

To ensure future ARDS definitions remain clinically relevant, they must integrate not only physiological parameters but also emerging biomarkers, genetic profiles, and precise subphenotyping to guide individualized treatment. This precision-driven approach shifts the focus from generalized supportive care to targeted interventions that address the syndrome's underlying pathology. Enhanced definitions incorporating these diverse elements could enable earlier recognition, optimize treatment strategies, and ultimately improve survival and recovery for patients with ARDS—advancing both the field of critical care and patient outcomes.

Abbreviations

AECC	American-European consensus conference
APRV	Airway pressure release ventilation
ARDS	Acute respiratory distress syndrome
ASV	Adaptive support ventilation
ATS	American thoracic society
CARDS	COVID-19-associated ARDS
ECMO	Extracorporeal membrane oxygenation
ESICM	European society of intensive care medicine
FiO_2	Inspired oxygen fraction
HFNO	High-flow nasal oxygen
LIS	Lung injury score
PaO_2	Arterial oxygen pressure
PEEP	Positive end-expiratory pressure
RMs	Recruitment maneuvers
RV	Right ventricular
SpO_2	Peripheral oxygen saturation
TCAV	Time-controlled adaptive ventilation
VILI	Ventilator-induced lung injury

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Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
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